Published in final edited form as:

Clin Perinatol. 2012 March ; 39(1): 239–254. doi:10.1016/j.clp.2011.12.013.

Anesthesia and Analgesia in the NICU

R. Whit Hall, MD

Division of Neonatology, University of Arkansas for Medical Sciences, Slot 512B, 4301 West Markham, Little Rock, AR 72205, USA, hallrichmanw@uams.edu

Keywords

Anesthesia; Analgesia; NICU; Pain management; Infant newborn; Infant premature

Pain management is increasingly recognized as an integral part of effective management of vulnerable babies in the neonatal intensive care unit (NICU). Traditionally, neonates have not been accorded the same respect for pain as have their older counterparts because pain, as defined by the International Association for the Study of Pain, is “always subjective.” Babies requiring intensive care are unable to express discomfort. Furthermore, preterm neonates in particular do not have the strength to protest like older children or even term neonates. The parents, who would advocate for their babies, are often asked to wait outside the NICU while painful procedures are being performed (despite evidence that pain can be mitigated by parental involvement¹). Furthermore, neonates do not fill out satisfaction surveys or express displeasure as a result of being exposed to painful stimuli, making them at risk for inadequate pain treatment.

Before 1980, pain in the newborn period was infrequently recognized or treated.² Because the gold standard of pain assessment is self-reporting, which is clearly not possible in the newborn period, clinicians can only measure pain indirectly. Animal and human studies have documented that neonatal pain is associated with short- and long-term adverse consequences.^{3,4} Furthermore, the enhanced survival of extremely low-birth-weight babies makes them more susceptible to the effects of pain and stress because of increased exposure. Indeed, one study documented that neonates less than 32 weeks’ gestation were exposed to 10 to 15 painful procedures per day, up to 22 procedures per day in the first 2 weeks of life,⁵ and most of these procedures were untreated.⁶ Clinicians advocating pain relief continue to struggle. A recent study by Carbajol and colleagues⁷ has documented the increased occurrence and lack of treatment of neonatal pain in almost 80% of newborns in intensive care.

Analgesia and sedation in the NICU has been fraught with controversy because of concern about the safety of these drugs in the neonatal population, lack of adequate pharmacokinetic and pharmacodynamic data in this population, difficulty in pain assessment, and lack of long-term neurodevelopmental assessment of survivors for the pain experienced in the neonatal period.^{8–11} Legitimate concern about safety has led to more governance for moderate sedation privileges for clinicians caring for neonates and more emphasis on obtaining consent for sedation,¹² leading to roadblocks to giving sedation to neonates undergoing painful procedures. Furthermore, individual differences and decreased morphine metabolism in younger gestational age neonates may lead to the rapid development of tolerance and accumulation of the drug in extremely preterm neonates.¹³ Thus, the use of sedation and analgesia in the neonatal population although extremely important, must be done safely and effectively (Table 1).

In a practical sense, every NICU should have a program to reduce pain for the NICU patient. This program should include a comprehensive approach, as shown in Fig. 1. A stepwise approach should begin with avoidance of painful procedures as much as possible, followed by nonpharmacologic and then pharmacologic methods for pain relief. Because the projected pain is expected to become more severe, increasingly potent drugs (with increasing complications) should be used. An effective pain relief program also provides education for all healthcare providers.^{27,28}

NEONATAL PAIN ASSESSMENT

Pain assessment has been termed the “fifth vital sign” by the Joint Commission for the Accreditation of Hospitals. However, the gold standard is self-reporting, obviously not possible in neonates. Therefore, several pain assessment tools (>40 and still counting) have been developed for this purpose.¹⁰ Pain assessment is based on physiologic (heart rate, blood pressure, respiratory rate, and oxygen saturation) and behavioral (facial action, body movements, and cry) measures. Behavioral measures are more pain specific,²⁹ whereas physiologic measures are more indicative of stress and not as specific for pain.³⁰ Unfortunately, there is poor correlation between these two measurements,³¹ and neonatal pain assessment remains controversial. Furthermore, preterm neonates exhibit differential responses to pain as evidenced by the different pain scores in the Premature Infant Pain Profile, one of the pain assessment tools commonly used in NICUs.³² Clearly, the metabolic cost of mounting a robust response to pain for an extremely preterm neonate is not worth the energy expenditure given the limited energy reserves.³³

Almost all pain assessment scores have been developed for acute pain in neonates, but chronic pain is common and important for neonatal assessment. Assisted ventilation, necrotizing enterocolitis, and postsurgical trauma are all chronic painful conditions in need of treatment. To date, only two pain assessment tools have been validated for chronic neonatal pain: the Neonatal Pain and Discomfort Scale³⁴ and the Echelle Douleur Inconfort Nouveau-Ne Scale.³⁵ Although there are advocates for each of these pain scales, it is more important for providers to become familiar with at least one scale that can be used to assess acute and chronic pain and assess neonates of different gestational ages.

NONPHARMACOLOGIC METHODS

Nonpharmacologic pain treatment in neonates has been clearly demonstrated to relieve mild to moderate pain. The best studied techniques include nonnutritive sucking (with and without sucrose); breastfeeding; swaddling; kangaroo care (skin-to-skin contact); and massage therapy. Nonnutritive sucking and sucrose work by increasing endogenous endorphins. Although sucrose has been shown to enhance effectiveness, they have both been shown to decrease crying time and improve pain scores after acute mild pain, such as heel-stick pain.^{36–38} Sucrose is efficacious in reducing the pain from single events, such as retinopathy of prematurity screening,^{39,40} oral gastric tube insertion,⁴¹ and heel lance.⁴² However, sucrose is controversial when given repeatedly, possibly leading to adverse long-term outcomes.⁴³ Kangaroo care, which was first used in developing countries to decrease neonatal mortality, has also been shown to relieve neonatal pain. Kangaroo care decreases the pain associated with single procedures, such as heel lance,^{44,45} but the magnitude of the effect is unknown.⁴⁶ Swaddling decreases acute mild-to-moderate pain, such as the pain associated with heel-lance procedures.⁴⁷ Massage therapy has been inadequately studied; however, it has shown promise in ameliorating heel-stick pain⁴⁸ and it is effective in multisensorial stimulation.⁴⁹ Nonpharmacologic techniques are safe and have demonstrated effectiveness in relieving mild-to-moderate neonatal pain associated with single procedures.

These methods generally require parental involvement; thus, family centered care in the NICU should be encouraged to ameliorate neonatal pain.

PHARMACOLOGIC METHODS

Opioids

Opioids are commonly used in modern NICUs.⁵⁰ They provide procedural pain relief, such as for intubation premedication^{51–53}; relief from chronic pain, such as necrotizing enterocolitis⁵⁴; and ventilation.^{16,55,56} Several studies and reviews have pointed to the conclusion that they should be used selectively. A recent Cochrane review found insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns.⁵⁶ The Cochrane review looked at pain scales, and overall found that a significant effect on pain was found in the treatment group. No significant effect was found in favor of the treatment group with respect to neonatal mortality; duration of ventilation; neurodevelopmental outcome, short-term and long-term; incidence of severe intraventricular hemorrhage (IVH); any IVH; and periventricular leukomalacia (PVL). Given the likely long-term adverse consequences associated with the chronic pain and stress of mechanical ventilation, it is reassuring that short-term adverse effects are not more common in the opioid-treated groups.

Morphine—Morphine is the most frequently used opioid analgesic in all ages, and is the most commonly used drug for analgesia in ventilated neonates.⁵⁰ Morphine has a slow onset of analgesia. Its mean onset of action is 5 minutes and the peak effect is at 15 minutes. It is metabolized in the liver into two active compounds: morphine-3-glucuronide and morphine-6-glucuronide. The former is an opioid antagonist, and the latter is a potent analgesic. Preterm infants mostly produce morphine-3-glucuronide, which explains why after 3 to 4 days of morphine therapy, the infant develops tolerance.⁵⁷ Side-effects of morphine include hypotension in neonates with pre-existing hypotension and gestational age less than 26 weeks,¹⁷ prolonged need for assisted ventilation, and increased time to reach full feeds.^{16,55} Others have suggested that morphine may have a specific effect on pulmonary mechanics, possibly caused by undefined direct toxicity, such as histamine release or bronchospasm.⁵⁸ Although commonly used, there is controversy as to whether morphine is effective in the treatment of acute pain.⁵⁹

Two large randomized studies have compared morphine with placebo in neonates. A randomized controlled trial conducted in the Netherlands compared the analgesic effect of morphine with placebo infusions for the duration of 7 days in 150 newborns who received mechanical ventilation. The findings of this study suggested that routine morphine infusion in preterm newborns who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome, defined as severe IVH, PVL, or death within 28 days.⁵⁵ The Neurologic Outcomes and Preemptive Analgesia in Neonates trial included ventilated preterm neonates from 16 centers in the United States and Europe. It compared the effect of morphine with placebo infusions, after a loading dose, on the neurologic outcomes of the ventilated neonates. The results suggested that continuous morphine infusion did not reduce early neurologic injury in ventilated preterm neonates, defined as severe IVH, PVL, or death.^{16,60} Hypotension did occur more frequently in the morphine versus the placebo group.

One study assessed the long-term outcome at 5 to 6 years of prematurely born children (<34 weeks of gestation) who by randomization received morphine in the neonatal period to facilitate mechanical ventilation. This study looked at children from two trials. The first one included 95 infants who were randomly assigned to receive morphine alone, pancuronium alone, or morphine and pancuronium. The second trial included 21 infants who received morphine and 20 infants who received placebo. Each child was assessed using three scales:

the full scale Weschler Preschool and Primary Scale of Intelligence, the Movement Assessment Battery for Children, and the Child Behavior Checklist. There were no adverse effects found on intelligence, motor function, or behavior.⁶¹

Fentanyl—Fentanyl is an opioid analgesic that is 50 to 100 times more potent than morphine.⁶² It is used frequently because of its ability to provide rapid analgesia.⁶³ It may be used as a slow intravenous push every 2 to 4 hours or as a continuous infusion. Tolerance may develop and withdrawal symptoms may occur after 5 days or more of continuous infusions.⁶² In a masked randomized controlled trial, a single dose of fentanyl given to ventilated preterm newborns significantly reduced pain behaviors and changes in heart rate. It also increased growth hormone levels.⁶⁴ In another study, fentanyl provided the same pain relief as morphine but with fewer side effects.⁶⁵ In other studies, fentanyl use resulted in lower heart rates, behavioral stress scores, and pain scores compared with placebo; however, the infants receiving fentanyl required higher ventilator rates and peak inspiratory pressures at 24 hours.⁶⁶ Fentanyl may also be used transdermally in patients with limited intravenous access. Side effects of fentanyl include bradycardia, chest wall rigidity, and opioid tolerance after prolonged therapy.

Methadone—Methadone is a potent analgesic with a rapid onset of action and prolonged effect.⁶³ It has minimal side effects, high enteral bioavailability, and a low cost.

Other opiates—Other opiates include the short-acting drugs sulfentanil, alfentanil, and remifentanil. All are useful for short procedures, such as intubation. Sulfentanil and alfentanil are metabolized by the liver, which is immature in preterm neonates resulting in increased levels with repeated infusions, especially in preterm neonates.⁶⁷ Remifentanil, however, is rapidly cleared by plasma esterases and is unaffected by the maturity of the liver enzyme system, making it attractive for short neonatal surgery or other procedures when rapid recovery is anticipated (Table 2).⁶⁷

Benzodiazepines

The benzodiazepines are anxiolytic drugs that have limited analgesic effect but are commonly used in NICUs to produce sedation, muscle relaxation, and provide amnesia (in older patients), but they provide little analgesia. This class of drugs inhibits γ -aminobutyric acid A receptors.⁶⁸ The main complications include myoclonic jerking, excessive sedation, respiratory depression, and occasional hypotension.

Midazolam—The most commonly used benzodiazepine in the NICU is midazolam. When administered with morphine, it has been shown to provide better sedation than morphine alone in ventilated patients, without adverse effects.⁶⁹ The minimal effective dose for most neonates is 200 $\mu\text{g/kg}$ with a maintenance dose of 100 $\mu\text{g/kg/h}$.⁷⁰ Although it can be given orally, the bioavailability is only half that of intravenous midazolam in neonates.⁷¹ Intranasal midazolam has been shown to be effective for fundoscopic examinations in older children, but this mode of delivery has not been tested in neonates.⁷² One recent review found no apparent clinical benefit of midazolam compared with opiates in mechanically ventilated neonates.⁷³ Furthermore, midazolam was associated with worse short-term adverse effects (death, severe IVH, or PVL) in the NOPAIN trial compared with morphine alone.¹⁸ Midazolam seems to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone. The decreased number of γ -aminobutyric acid A receptors in neonates compared with adults may contribute to the neonate's risk of neuroexcitability and clonic activity that resembles and, in some cases may be, seizure activity.⁷⁴ Finally, metabolism for these drugs occurs through glucuronidation (hydroxymidazolam) in the liver, and there is

potential for decreased bilirubin metabolism, especially in asphyxiated or preterm newborns. Its half-life is only 30 to 60 minutes, but it may be prolonged in preterm and sick neonates. Thus, pharmacokinetic and pharmacodynamic data are unreliable in sick neonates and drug levels correlate poorly with sedative effects, so it should be titrated using a validated pain scale.^{75,76} Although there are relatively few studies to support the use of midazolam in neonates, it is common practice to use this drug as a sedative for ventilated neonates and for procedural pain.⁷⁷ A Cochrane report described only three trials using this drug, which could not be combined for analysis because of different tools used to assess sedation.⁷⁸ There are some concerns regarding the use of midazolam in neonates. One study reported an increased incidence of adverse short-term effects (IVH, PVL, or death) and a longer hospital stay associated with midazolam.¹⁸ Finally, midazolam has been associated with benzyl alcohol exposure.⁷⁹ There have been no long-term studies describing benefit or harm with midazolam. It has been shown (along with morphine) to adhere to the tubing in patients on extracorporeal membrane oxygenation, increasing dosing requirements by 50% in those patients.⁸⁰

Lorazepam—Lorazepam has also been used in the intensive care nursery. Because it is a longer-acting drug than midazolam with a duration of action of 8 to 12 hours, it does not have to be given as a drip or as frequently. It has been used successfully for seizure control in neonates who are refractory to phenobarbital and phenytoin despite its potential neuronal toxicity.⁸¹ It has been associated with propylene glycol exposure (Table 3).⁷⁹

Barbiturates

Phenobarbital—Phenobarbital is usually considered the drug of choice for seizure control. Despite animal evidence for antinociception, it is often used for analgesia.⁸² It is also used in conjunction with opioids for sedation,¹⁶ although there is little recent evidence that it is effective. Classically, it has been used for neonatal abstinence syndrome, but recent work by Ebner and coworkers⁸³ demonstrates that opiates shorten the time required for treatment. However, because of its anticonvulsant effects, phenobarbital is an attractive adjunct for patients with seizures.

Chloral Hydrate

Chloral hydrate is commonly used in neonatal intensive care when sedation, particularly sleep, is required without analgesia. It is commonly used for radiologic procedures, electroencephalography, echocardiography, and dental procedures in older patients. It is converted to trichloroethanol, which is also metabolically active.⁸⁴ A recent retrospective review found an increased incidence of apnea and desaturation in term neonates less than 1 month and in preterm neonates less than 60 weeks post-conceptual age who underwent magnetic resonance imaging.⁸⁵ Thus, this drug should be used with caution in preterm and young term neonates.

Propofol

Propofol has become popular as an anesthetic agent for young children, but it has not been studied extensively in neonates.^{86–88} One study compared propofol with morphine, atropine, and suxamethonium for intubation and found that propofol led to shorter intubation times, higher oxygen saturations, and less trauma than the combination regimen in neonates.⁸⁹ However, propofol should be used with caution in young infants because clearance is inversely related to neonatal and postmenstrual age. There is significant interindividual variability in the pharmacokinetics of propofol in that population⁹⁰ and its use has led to transient decreases in heart rate and oxygen saturation and more prolonged (60 minutes) hypotension.⁹¹

Ketamine

Ketamine is a dissociative anesthetic that provides analgesia, amnesia, and sedation. Ketamine has been studied and used extensively in older children,⁹² but there have been few studies in newborns. Ketamine causes mild increases in blood pressure and heart rate, decreases in respiratory drive, and mild bronchodilation⁹³ with minimal effects on cerebral blood flow,⁹⁴ making it an attractive choice for some unstable hypotensive neonates requiring procedures, such as cannulation for extracorporeal membrane oxygenation.⁹⁴ Doses for effective pain management of the pain caused by endotracheal suctioning in ventilated neonates were 2 mg/kg in one Finnish study.⁹⁵ It has also been shown to decrease inflammatory cell death in the presence of pain in immature rodents in the author's laboratory, which would also make it attractive for preterm neonates, although this has not been shown in human studies.⁹⁶ Despite these theoretical advantages, ketamine is a potent anesthetic with minimal study in neonates. As such, it should only be used for highly invasive procedures.

Acetaminophen

Acetaminophen acts by inhibiting the cyclooxygenase (COX) enzymes in the brain, and it has been well studied in newborns.⁵⁴ It is useful for mild pain, in conjunction with other pain relief, or after circumcision.⁹⁷

Local Anesthetics

Lidocaine—Lidocaine inhibits axonal transmission by blocking Na⁺ channels. Lidocaine is commonly used for penile blocks for circumcisions. In this circumstance, its use has demonstrated effectiveness in decreasing pain response to immunizations as long as 4 months after circumcision compared with neonates who received placebo.¹⁹ Compared with a dorsal penile root block or eutectic mixture of local anesthetics cream, the ring block has been shown to be the most effective means of pain relief for circumcision.⁹⁸

Topical anesthetics—Topical anesthetics have demonstrated effectiveness for certain types of procedural pain, such as venipuncture,⁹⁹ lumbar puncture,¹⁰⁰ or immunizations.¹⁰¹ Complications include methemoglobinemia and transient skin rashes.¹⁰² In preterm neonates with thin skin the concern for methemoglobinemia is accentuated.

Unfortunately, topical anesthetics have not been effective in providing pain relief for the heel prick, one of the most common skin-breaking procedures, because of increased skin thickness.¹⁰³ Newer topical anesthetics include 4% tetracaine and 4% liposomal lidocaine. Although the newer agents have a shorter onset of action, they are no more effective.

COMMON PROCEDURES

Common neonatal procedures and advantages and disadvantages of pain relief are summarized in Table 4.

FUTURE DIRECTIONS

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are used extensively for pain relief in children and adults but they are mainly used for patent ductus arteriosus closure in neonates. They act by inhibiting the COX enzymes (COX-1 and COX-2) responsible for converting arachidonic acid into prostaglandins, thus producing their analgesic, antipyretic, and anti-inflammatory effects.⁶³ The analgesic effects of nonsteroidal anti-inflammatory drugs have not been studied in neonates, although ibuprofen and indomethacin have been studied for use in

patent ductus arteriosus closure. Concern about side effects of renal dysfunction, platelet adhesiveness, and pulmonary hypertension has limited their study for this indication.^{73,111,112} However, ibuprofen has demonstrated beneficial effects on cerebral circulation in human studies¹¹³ and beneficial effects on the development of chronic lung disease in baboon experiments,¹¹⁴ making it an attractive analgesic in preterm neonates.

Nonpharmacologic Methods

Nonpharmacologic approaches, such as acupuncture and music, may be effective, but their use in acute pain relief needs further research.¹¹⁵ Music has beneficial effects on mothers, but it has not yet been shown to consistently relieve pain.¹¹⁶ Acupuncture has been studied extensively in older children and adults but it has not yet been studied in neonates.¹¹⁷ Acupuncture, especially electroacupuncture, has great potential to relieve neonatal pain, but it has also been inadequately studied.¹¹⁸

Quality Improvement Approach

A suggested approach to evidence-based recommendations for the treatment of neonatal pain includes the following:

1. Recognition of neonatal pain as a valid concern
2. Recognition of acute procedural and chronic neonatal pain in need of treatment
3. Validated assessment tool for neonatal pain
4. Educational resources for caregivers and parents in the NICU
5. Protocolized stepwise treatment plan for the procedures and conditions encountered in the NICU using nonpharmacologic and pharmacologic approaches to treatment
6. Continued auditing to ascertain appropriate treatment for neonatal pain
7. A well-planned program of coordination, facilitation, and using local champions and project teams to elicit a beneficial change in practice.¹¹⁹

Acknowledgments

Supported in part by NCRR Grant 20146.

REFERENCES

1. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci*. 2001; 24:1161–1192. [PubMed: 11520931]
2. Anand KJ, Hall RW. Controversies in neonatal pain: an introduction. *Semin Perinatol*. 2007; 31(5): 273–274. [PubMed: 17905180]
3. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med*. 1987; 317(21):1321–1329. [PubMed: 3317037]
4. Fumagalli F, Moteni R, Racagni G, et al. Stress during development: impact on neuroplasticity and relevance to psychopathology. *Prog Neurobiol*. 2007; 81(4):197–217. [PubMed: 17350153]
5. Cignacco E, Hamers J, van Lingen RA, et al. Neonatal procedural pain exposure and pain management in ventilated preterm infants during the first 14 days of life. *Swiss Med Weekly*. 2009; 139(15–16):226–232.
6. Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. *Arch Dis Child Fetal Neonatal Ed*. 1995; 72(1):F47–F48. [PubMed: 7743285]
7. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA*. 2008; 300(1):60–70. [PubMed: 18594041]

8. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet*. 1996; 31(6):423–443. [PubMed: 8968656]
9. Anand KJ, Aranda JV, Berde CB, et al. Summary proceedings from the neonatal pain-control group. *Pediatrics*. 2006; 117(3 Pt 2):S9–S22. [PubMed: 16777824]
10. Ranger M, Johnston CC, Anand KJ. Current controversies regarding pain assessment in neonates. *Semin Perinatol*. 2007; 31(5):283–288. [PubMed: 17905182]
11. Whitfield MF, Grunau RE. Behavior, pain perception, and the extremely low-birth weight survivor. *Clin Perinatol*. 2000; 27(2):363–379. [PubMed: 10863655]
12. Coté CJ, et al. American Academy of Pediatrics, American Academy of Pediatric Dentistry; Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics*. 2006; 118(6):2587–2602. [PubMed: 17142550]
13. Saarenmaa E, Neuvonen PJ, Rosenberg P, et al. Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther*. 2000; 68(2):160–166. [PubMed: 10976547]
14. VanLooy JW, Schumacher RE, Bhatt-Mehta V. Efficacy of a premedication algorithm for nonemergent intubation in a neonatal intensive care unit. *Ann Pharmacother*. 2008; 42(7):947–955. [PubMed: 18594052]
15. Anand KJ. The stress response to surgical trauma: from physiological basis to therapeutic implications. *Prog Food Nutr Sci*. 1986; 10(1–2):67–132. [PubMed: 3097757]
16. Anand KJ, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004; 363(9422):1673–1682. [see comment]. [PubMed: 15158628]
17. Hall RW, Kronsberg SS, Barton BA, et al. Morphine, hypotension, and adverse outcomes in preterm neonates: who's to blame? *Pediatrics*. 2005; 115(5):1351–1359. [PubMed: 15867047]
18. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. *Neonatal Outcome and Prolonged Analgesia in Neonates*. *Arch Pediatr Adolesc Med*. 1999; 153(4):331–338. [erratum appears in *Arch Pediatr Adolesc Med* 1999;153(8):895]. [PubMed: 10201714]
19. Taddio A, Katz J, Ilersich AL, et al. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet*. 1997; 349(9052):599–603. [PubMed: 9057731]
20. Grunau RE, Weinberg J, Whitfield MF. Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. *Pediatrics*. 2004; 114(1):e77–e84. [PubMed: 15231977]
21. Anand KJ, Anderson BJ, Holford NHG, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth*. 2008; 101(5):680–689. [PubMed: 18723857]
22. Grunau RE, Haley DW, Whitfield MF, et al. Altered basal cortisol levels at 3, 6, 8 and 18 months in infants born at extremely low gestational age. *J Pediatr*. 2007; 150(2):151–156. [PubMed: 17236892]
23. Bekhit MH. Opioid-induced hyperalgesia and tolerance. *Am J Ther*. 2010; 17(5):498–510. [PubMed: 20844348]
24. Bhutta AT, Venkatesan AK, Rovnaghi CR, et al. Anaesthetic neurotoxicity in rodents: is the ketamine controversy real? *Acta Paediatr*. 2007; 96(11):1554–1556. [PubMed: 17714546]
25. Zou X, Patterson TA, Divine RL, et al. Potential neurotoxicity of ketamine in the developing rat brain. *Toxicol Sci*. 2009; 108(1):149–158. [PubMed: 19126600]
26. Anand KJ, Hall RW. Love, pain, and intensive care. *Pediatrics*. 2008; 121(4):825–827. [PubMed: 18381545]
27. Schultz M, Loughran-Fowlds A, Spence K. Neonatal pain: a comparison of the beliefs and practices of junior doctors and current best evidence. *J Paediatr Child Health*. 2010; 46(1–2):23–28. [PubMed: 19943866]
28. Polkki T, Korhonen A, Laukkala S, et al. Nurses' attitudes and perceptions of pain assessment in neonatal intensive care. *Scand J Caring Sci*. 2010; 24(1):49–55. [PubMed: 20070593]
29. Craig KD, Whitfield MF, Grunau RV, et al. Pain in the preterm neonate: behavioural and physiological indices. *Pain*. 1993; 52(3):287–299. [erratum appears in *Pain* 1993;54(1):111]. [PubMed: 8460047]

30. Stevens BJ, Johnston CC. Physiological responses of premature infants to a painful stimulus. *Nurs Res.* 1994; 43(4):226–231. [PubMed: 8047427]
31. Johnston CC, Stevens BJ, Yang F, et al. Differential response to pain by very premature neonates. *Pain.* 1995; 61(3):471–479. [PubMed: 7478691]
32. Stevens B, Johnston C, Petryshen P, et al. Premature infant pain profile: development and initial validation. *Clin J Pain.* 1996; 12(1):13–22. [PubMed: 8722730]
33. Barr RG. Reflections on measuring pain in infants: dissociation in responsive systems and honest signalling. *Arch Dis Child Fetal Neonatal Ed.* 1998; 79(2):F152–F156. [PubMed: 9828746]
34. Hummel P, Puchalski M, Creech SD, et al. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. *J Perinatol.* 2008; 28(1):55–60. [PubMed: 18165830]
35. Debillon T, Bureau V, Savagner C, et al. Pain management in French neonatal intensive care units. *Acta Paediatr.* 2002; 91(7):822–826. [PubMed: 12200910]
36. Corbo MG, Mansi G, Stagni A, et al. Nonnutritive sucking during heelstick procedures decreases behavioral distress in the newborn infant. *Biol Neonate.* 2000; 77(3):162–167. [PubMed: 10729719]
37. Gibbins S, Stevens B, Hodnett E, et al. Efficacy and safety of sucrose for procedural pain relief in preterm and term neonates. *Nurs Res.* 2002; 51(6):375–382. [PubMed: 12464757]
38. Mitchell A, Waltman PA. Oral sucrose and pain relief for preterm infants. *Pain Manag Nurs.* 2003; 4(2):62–69. [PubMed: 12836150]
39. O'Sullivan A, O'Connor M, Brosnahan D, et al. Sweeten, soother and swaddle for retinopathy of prematurity screening: a randomised placebo controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2010; 95(6):F419–F422. [PubMed: 20876596]
40. Sun X, Lemyre B, Barrowman N, et al. Pain management during eye examinations for retinopathy of prematurity in preterm infants: a systematic review. *Acta Paediatr.* 2010; 99(3):329–334. [PubMed: 19958293]
41. Kristoffersen L, Skogvoll E, Hafstrom M. Pain reduction on insertion of a feeding tube in preterm infants: a randomized controlled trial. *Pediatrics.* 2011; 127(6):e1449–e1454. [PubMed: 21536607]
42. Johnston CC, Filion F, Campbell-Yeo M, et al. Enhanced kangaroo mother care for heel lance in preterm neonates: a crossover trial. *J Perinatol.* 2009; 29(1):51–56. [PubMed: 18769382]
43. Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. *Pediatrics.* 2010; 125(5):1042–1047. [PubMed: 20403938]
44. Cong X, Ludington-Hoe SM, McCain G, et al. Kangaroo care modifies preterm infant heart rate variability in response to heel stick pain: pilot study. *Early Hum Dev.* 2009; 85(9):561–567. [PubMed: 19505775]
45. Freire NB, Garcia JB, Lamy ZC. Evaluation of analgesic effect of skin-to-skin contact compared to oral glucose in preterm neonates. *Pain.* 2008; 139(1):28–33. [PubMed: 18434021]
46. Warnock FF, Castral TC, Brant R, et al. Brief report: maternal kangaroo care for neonatal pain relief: a systematic narrative review. *J Pediatr Psychol.* 2010; 35(9):975–984. [PubMed: 20040606]
47. Morrow C, Hiding A, Wilkinson-Faulk D. Reducing neonatal pain during routine heel lance procedures. *MCN Am J Matern Child Nurs.* 2010; 35(6):346–354. [quiz: 354–6]. [PubMed: 20926970]
48. Jain S, Kumar P, McMillan DD. Prior leg massage decreases pain responses to heel stick in preterm babies. *J Paediatr Child Health.* 2006; 42(9):505–508. [PubMed: 16925535]
49. Bellieni CV, Bagnoli F, Perrone S, et al. Effect of multisensory stimulation on analgesia in term neonates: a randomized controlled trial. *Pediatr Res.* 2002; 51(4):460–463. [PubMed: 11919330]
50. Hall RW, Boyle E, Young T. Do ventilated neonates require pain management? *Semin Perinatol.* 2007; 31(5):289–297. [PubMed: 17905183]
51. Whyte S, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units. *Arch Dis Child Fetal Neonatal Ed.* 2000; 82(1):F38–F41. [see comment]. [PubMed: 10634840]

52. Roberts KD, Leone TA, Edwards WH, et al. Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. *Pediatrics*. 2006; 118(4):1583–1591. [PubMed: 17015550]
53. Sarkar S, Schumacher RE, Baumgart S, et al. Are newborns receiving premedication before elective intubation? *J Perinatol*. 2006; 26(5):286–289. [PubMed: 16598295]
54. Menon G, Anand KJ, McIntosh N. Practical approach to analgesia and sedation in the neonatal intensive care unit. *Semin Perinatol*. 1998; 22(5):417–424. [PubMed: 9820566]
55. Simons SH, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA*. 2003; 290(18):2419–2427. [PubMed: 14612478]
56. Bellu R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2008; 1 CD004212.
57. Anand KJ. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *J Perinatol*. 2007; 27(Suppl 1):S4–S11. [PubMed: 17453028]
58. Levene M. Morphine sedation in ventilated newborns: who are we treating? *Pediatrics*. 2005; 116(2):492–493. [comment]. [PubMed: 16061608]
59. Carbajal R, Lenclen R, Jugie M, et al. Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates. *Pediatrics*. 2005; 115(6):1494–1500. [PubMed: 15930209]
60. Bhandari V, Bergqvist LL, Kronsberg SS, et al. Morphine administration and short-term pulmonary outcomes among ventilated preterm infants. *Pediatrics*. 2005; 116(2):352–359. [see comment]. [PubMed: 16061589]
61. MacGregor R, Evans D, Sugden D, et al. Outcome at 5–6 years of prematurely born children who received morphine as neonates. *Arch Dis Child Fetal Neonatal Ed*. 1998; 79(1):F40–F43. [PubMed: 9797623]
62. Mitchell A, Brooks S, Roane D. The premature infant and painful procedures. *Pain Manag Nurs*. 2000; 1(2):58–65. [PubMed: 11706460]
63. Anand KJ, Hall RW. Pharmacological therapy for analgesia and sedation in the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2006; 91(6):F448–F453. [erratum appears in *Arch Dis Child Fetal Neonatal Ed* 2007;92(2):F156; note dosage error in text]. [PubMed: 17056842]
64. Guinsburg R, Kopelman BI, Anand KJ, et al. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. *J Pediatr*. 1998; 132(6):954–959. [PubMed: 9627585]
65. Saarenmaa E, Huttunen P, Leppaluoto J, et al. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomized trial. *J Pediatr*. 1999; 134(2):144–150. [see comment]. [PubMed: 9931520]
66. Orsini AJ, Leef KH, Costarino A, et al. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. *J Pediatr*. 1996; 129(1):140–145. [see comment]. [PubMed: 8757574]
67. Berde CB, Jaksic T, Lynn AM, et al. Anesthesia and analgesia during and after surgery in neonates. *Clin Ther*. 2005; 27(6):900–921. [PubMed: 16117991]
68. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet*. 1998; 35(1):37–47. [PubMed: 9673833]
69. Arya V, Ramji S. Midazolam sedation in mechanically ventilated newborns: a double blind randomized placebo controlled trial. *Indian Pediatr*. 2001; 38(9):967–972. [see comment]. [PubMed: 11568372]
70. Treluyer JM, Zohar S, Rey E, et al. Minimum effective dose of midazolam for sedation of mechanically ventilated neonates. *J Clin Pharm Ther*. 2005; 30(5):479–485. [PubMed: 16164495]
71. de Wildt SN, Kearns GL, Hop WC, et al. Pharmacokinetics and metabolism of oral midazolam in preterm infants. *Br J Clin Pharmacol*. 2002; 53(4):390–392. [PubMed: 11966671]
72. Altintas O, Karabas VL, Demirci G, et al. Evaluation of intranasal midazolam in refraction and fundus examination of young children with strabismus. *J Pediatr Ophthalmol Strabismus*. 2005; 42(6):355–359. [PubMed: 16382560]

73. Aranda JV, Carlo W, Hummel P, et al. Analgesia and sedation during mechanical ventilation in neonates. *Clin Ther.* 2005; 27(6):877–899. [PubMed: 16117990]
74. Chess PR, D'Angio CT. Clonic movements following lorazepam administration in full-term infants. *Arch Pediatr Adolesc Med.* 1998; 152(1):98–99. [PubMed: 9452719]
75. Ahsman MJ, Hanekamp M, Wildschut ED, et al. Population pharmacokinetics of midazolam and its metabolites during venoarterial extracorporeal membrane oxygenation in neonates. *Clin Pharmacokinet.* 2010; 49(6):407–419. [PubMed: 20481651]
76. de Wildt SN, de Hoog M, Vinks AA, et al. Pharmacodynamics of midazolam in pediatric intensive care patients. *Ther Drug Monit.* 2005; 27(1):98–102. [PubMed: 15665754]
77. Benini F, Farina M, Capretta A, et al. Sedoanalgesia in paediatric intensive care: a survey of 19 Italian units. *Acta Paediatr.* 2010; 99(5):758–762. [PubMed: 20136798]
78. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database Syst Rev.* 2003; 1 CD002052.
79. Shehab N, Lewis CL, Streetman DD, et al. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med.* 2009; 10(2): 256–259. [PubMed: 19188870]
80. Bhatt-Meht V, Annich G. Sedative clearance during extracorporeal membrane oxygenation. *Perfusion.* 2005; 20(6):309–315. [PubMed: 16363315]
81. McDermott CA, Kowalczyk AL, Schnitzler ER, et al. Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr.* 1992; 120(3):479–483. [PubMed: 1538303]
82. Gonzalez-Darder JM, Ortega-Alvaro A, Ruz-Franzi I, et al. Antinociceptive effects of phenobarbital in “tail-flick” test and deafferentation pain. *Anesth Analg.* 1992; 75(1):81–86. [PubMed: 1616167]
83. Ebner N, Rohrmeister K, Winklbaier B, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend.* 2007; 87(2–3):131–138. [PubMed: 17000060]
84. Mayers DJ, Hindmarsh KW, Gorecki DK, et al. Sedative/hypnotic effects of chloral hydrate in the neonate: trichloroethanol or parent drug? *Dev Pharmacol Ther.* 1992; 19(2–3):141–146. [PubMed: 1340434]
85. Litman RS, Soin K, Salam A. Chloral hydrate sedation in term and preterm infants: an analysis of efficacy and complications. *Anesth Analg.* 2010; 110(3):739–746. [PubMed: 20032023]
86. Disma N, Astuto M, Rizzo G, et al. Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. *Eur J Anaesthesiol.* 2005; 22(11):848–852. [PubMed: 16225720]
87. Rigby-Jones AE, Nolan JA, Priston MJ, et al. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. *Anesthesiology.* 2002; 97(6):1393–1400. [PubMed: 12459664]
88. Jenkins IA, Playfor SD, Bevan C, et al. Current United Kingdom sedation practice in pediatric intensive care. *Paediatr Anaesth.* 2007; 17(7):675–683. [PubMed: 17564650]
89. Ghanta S, Abdel-Latif ME, Lui K, et al. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. *Pediatrics.* 2007; 119(6):e1248–e1255. [see comment]. [PubMed: 17485450]
90. Allegaert K, Peeters MY, Verbesselt R, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth.* 2007; 99(6):864–870. [PubMed: 17965417]
91. Vanderhaegen J, Naulaers G, Van Huffel S, et al. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. *Neonatology.* 2010; 98(1):57–63. [PubMed: 20051696]
92. Green SM, Denmark TK, Cline J, et al. Ketamine sedation for pediatric critical care procedures. *Pediatr Emerg Care.* 2001; 17(4):244–248. [PubMed: 11493822]
93. Chambliss CR, Anand KJ. Pain management in the pediatric intensive care unit. *Curr Opin Pediatr.* 1997; 9(3):246–253. [PubMed: 9229164]
94. Betremieux P, Carre P, Pladys P, et al. Doppler ultrasound assessment of the effects of ketamine on neonatal cerebral circulation. *Dev Pharmacol Ther.* 1993; 20(1–2):9–13. [PubMed: 7924769]

95. Saarenmaa E, Neuvonen PJ, Huttunen P, et al. Ketamine for procedural pain relief in newborn infants. *Arch Dis Child Fetal Neonatal Ed.* 2001; 85(1):F53–F56. [PubMed: 11420324]
96. Anand KJ, Soriano SG. Anesthetic agents and the immature brain: are these toxic or therapeutic? *Anesthesiology.* 2004; 101(2):527–530. [see comment]. [PubMed: 15277935]
97. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: the effect on pain. *Pediatrics.* 1994; 93(4):641–646. [PubMed: 8134222]
98. Lander J, Brady-Fryer B, Metcalfe JB, et al. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. *JAMA.* 1997; 278(24):2157–2162. [see comment]. [PubMed: 9417009]
99. Garcia OC, Reichberg S, Brion LP, et al. Topical anesthesia for line insertion in very low birth weight infants. *J Perinatol.* 1997; 17(6):477–480. [PubMed: 9447537]
100. Kaur G, Gupta P, Kumar A. A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Arch Pediatr Adolesc Med.* 2003; 157(11):1065–1070. [PubMed: 14609894]
101. Gradin M, Eriksson M, Holmqvist G, et al. Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics.* 2002; 110(6):1053–1057. [see comment]. [PubMed: 12456899]
102. Taddio A, Stevens B, Craig K, et al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med.* 1997; 336(17):1197–1201. [see comment]. [PubMed: 9110906]
103. Larsson BA, Norman M, Bjerring P, et al. Regional variations in skin perfusion and skin thickness may contribute to varying efficacy of topical, local anaesthetics in neonates. *Paediatr Anaesth.* 1996; 6(2):107–110. [PubMed: 8846274]
104. Pereira e Silva Y, Gomez RS, Barbosa RF, et al. Remifentanyl for sedation and analgesia in a preterm neonate with respiratory distress syndrome. *Paediatr Anaesth.* 2005; 15(11):993–996. [see comment]. [PubMed: 16238563]
105. Knolle E, Oehmke MJ, Gustorff B, et al. Target-controlled infusion of propofol for fiberoptic intubation. *Eur J Anaesthesiol.* 2003; 20(7):565–569. [PubMed: 12884991]
106. Singh A, Girotra S, Mehta Y, et al. Total intravenous anesthesia with ketamine for pediatric interventional cardiac procedures. *J Cardiothorac Vasc Anesth.* 2000; 14(1):36–39. [PubMed: 10698390]
107. Oklu E, Bulutcu FS, Yalcin Y, et al. Which anesthetic agent alters the hemodynamic status during pediatric catheterization? comparison of propofol versus ketamine. *J Cardiothorac Vasc Anesth.* 2003; 17(6):686–690. [see comment]. [PubMed: 14689405]
108. Bouwmeester NJ, Hop WC, van Dijk M, et al. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med.* 2003; 29(11):2009–2015. [PubMed: 12897995]
109. Simons SH, van Dijk M, Anand KS, et al. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med.* 2003; 157(11):1058–1064. [PubMed: 14609893]
110. McCarver-May DG, Kang J, Aouthmany M, et al. Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr.* 1996; 128(4):573–576. [see comment]. [PubMed: 8618198]
111. Allegaert K, Cossy V, Debeer A, et al. The impact of ibuprofen on renal clearance in preterm infants is independent of the gestational age. *Pediatr Nephrol.* 2005; 20(6):740–743. [PubMed: 15785936]
112. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev.* 2008; 1 CD003481.
113. Naulaers G, Delanghe G, Allegaert K, et al. Ibuprofen and cerebral oxygenation and circulation. *Arch Dis Child Fetal Neonatal Ed.* 2005; 90(1):F75–F76. [PubMed: 15613583]
114. McCurnin D, Seidner S, Chang LY, et al. Ibuprofen-induced patent ductus arteriosus closure: physiologic, histologic, and biochemical effects on the premature lung. *Pediatrics.* 2008; 121(5):945–956. [PubMed: 18450898]

115. Golianu B, Krane E, Seybold J, et al. Non-pharmacological techniques for pain management in neonates. *Semin Perinatol.* 2007; 31(5):318–322. [PubMed: 17905187]
116. Lai HL, Chen CJ, Peng TC, et al. Randomized controlled trial of music during kangaroo care on maternal state anxiety and preterm infants' responses. *Int J Nurs Stud.* 2006; 43(2):139–146. [PubMed: 15996669]
117. Wu MT, Sheen JM, Chuang KH, et al. Neuronal specificity of acupuncture response: a fMRI study with electroacupuncture. *Neuroimage.* 2002; 16(4):1028–1037. [PubMed: 12202090]
118. Woo YM, Lee MS, Nam Y, et al. Effects of contralateral electroacupuncture on brain function: a double-blind, randomized, pilot clinical trial. *J Altern Complement Med.* 2006; 12(8):813–815. [PubMed: 17034288]
119. Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health.* 2011; 47(3):92–98. [PubMed: 21091580]

Fig. 1.
Stepwise approach for the management of acute pain in neonates.

Table 1

Balance between treatment for pain and concerns regarding treatment

Reasons to Treat for Pain	Concerns Regarding Treatment
Beneficial short-term effects (less ventilator asynchrony, splinting, faster intubation, ¹⁴ decreased morbidity especially after surgery ¹⁵)	Adverse short-term effects (hypotension, respiratory depression, prolonged ventilator dependence, ^{16,17} intraventricular hemorrhage ¹⁸)
Beneficial long-term effects (improved response to pain, ¹⁹ downregulation of the hypopituitary-adrenal axis ²⁰)	Prolonged metabolism of opioids and benzodiazepines ²¹
Less stress associated with pain ²²	Hyperalgesia ²³
Decreased neuronal cell death in the presence of pain ²⁴	Enhanced neuronal cell death ²⁵
Compassion ²⁶	Unknown effects of commonly used drugs

Table 2

Summary of opiate drugs

Drug	Advantages	Disadvantages
Morphine	Potent pain relief Better ventilator synchrony Sedation Hypnosis Muscle relaxation Inexpensive	Respiratory depression Arterial hypotension Constipation, nausea Urinary retention Central nervous system depression Tolerance and dependence Long-term outcomes not studied Prolonged ventilator use
Fentanyl	Fast acting Less hypotension	Respiratory depression Short half-life Quick tolerance and dependence Chest wall rigidity Inadequately studied
Remifentanyl	Fast acting Degraded in the plasma Unaffected by liver metabolism	

Table 3**Benzodiazepines**

Drug	Advantages	Disadvantages
Benzodiazepines	Better ventilator synchrony Antianxiety Sedation Hypnosis Muscle relaxation Amnesia Anticonvulsant	No pain relief Arterial hypotension Respiratory depression Constipation and nausea Urinary retention Myoclonus Seizures Central nervous system depression Tolerance and dependence May interfere with bilirubin Metabolism Propylene glycol and benzyl alcohol exposure
Midazolam	Most studied benzodiazepine Quickly metabolized	Short acting
Lorazepam	Longer acting Better anticonvulsant	More myoclonus reported
Diazepam		Not recommended in the neonate

Table 4

Summary of procedures and recommendations for pain relief

Procedure	Drugs	Advantages of Treatment	Disadvantages of Treatment	Other Comments
Mechanical ventilation ^{16,55,56,65}	Fentanyl (1–3 µg/kg), morphine (0.1 mg/kg), midazolam (0.1–0.2 mg/kg)	Improved ventilator synchrony, lower pain scores	Prolonged time on assisted ventilation, prolonged time to full feeds, increased bladder catheterization, hypotension	Use sedation as needed, not pre-emptively; Midazolam associated with adverse short-term effects in NOPAIN Trial
Circumcision ^{98,102}	Lidocaine (1 mL), Eutectic mixture of local anesthetics	Less pain response up to 4 months postprocedure	Allergic reaction, bruising at injection site	Ring block is more effective than dorsal penile nerve root block
Heel lance ¹⁰³	Sucrose	Shorter crying, less changes in heart rate	None	Eutectic mixture of local anesthetics cream is not effective
Venipuncture, arterial puncture, and lumbar puncture ^{100,101}	Topical anesthetic (eutectic mixture of local anesthetics), sucrose	Lower premature infant pain profile scores, less crying	Local reaction, rare methemoglobinemia	Other nonpharmacologic treatments effective
Intubation ^{52,53,89,104,105}	Morphine 0.1 mg/kg, fentanyl 1–3 µg/kg, remifentanyl 1 mg/kg, midazolam 0.2 mg/kg, propofol 2–6 mg/kg, ketamine 1 mg/kg, suxamethonium 2 mg/kg	Shorter time to intubation, less trauma, less desaturation, better maintenance of vital signs	None	No accepted premedication Opiates most common class used
More invasive procedures, such as cannulation for extracorporeal membrane oxygenation ^{106,107}	Propofol 2–6 mg/kg, ketamine 1 mg/kg, fentanyl 1–3 µg/kg	Maintenance of cardiovascular stability	Questionable neurotoxicity with ketamine	Ketamine may be neuroprotective
Postsurgical pain ¹⁰⁸	Fentanyl 1–3 µg/kg, morphine 0.1 mg/kg, acetaminophen 15 mg/kg	Lowered neuroendocrine response, faster recovery	Respiratory depression, hypotension with opiates	Acetaminophen for mild pain only
Endotracheal suctioning ^{70,109}	Midazolam 0.2 mg/kg, morphine 0.1 mg/kg, fentanyl 1–3 µg/kg	Anxiolytic	Respiratory depression, hypotension, dependence	Usually not treated
Imaging (magnetic resonance imaging) ¹¹⁰	Chloral hydrate 50–100 mg/kg	Sedation	Respiratory depression, hypotension	Chloral hydrate provides sedation only